II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-49 were pending in the case at the time of the Office Action with claims 1-22, 39, 40, 42 and 48 having been withdrawn from consideration. No new claims have been added and no claims have been cancelled. Therefore, claims 23-38, 41-47 and 49 are under consideration.

Claim 23 has been amended to reflect the replication-competent nature of the adenoviral vectors relates, at a minimum, to cancer cells. See pages 12, 14 and 15 of the specification.

B. The Rejection of Claims Under 35 U.S.C. §112 is Overcome

Claims 28-31 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. More specifically, the claims recite the limitation of "said second therapy" and the independent claim is said to lack this limitation.

In response, Applicants have amended claims 28-31 to depend from claim 27, which includes the limitation of a second therapy. Therefore, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §112, second paragraph be withdrawn.

C. The Rejections of Claims Under 35 U.S.C. §103 Are Overcome

1. The Rejection of Claims Over Wold Taken With Walczak

Claims 23-38, 41, 43-47 and 49 have been rejected under 35 U.S.C. §103 over Wold *et al.* (U.S. Patent 6,627,190), hereinafter "Wold" taken with Walczak *et al.*, *Nat. Med.*, 5:157-163, 1999, hereinafter "Walczak." According to the Action, it would be

obvious to combine the adenoviral vector expressing ADP of Wold with TRAIL as taught by Walczak. Applicants respectfully traverse.

In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. *Manual of Patent Examining Procedure* §2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if one element is missing, a *prima facie* case of obviousness does not exist. Applicants submit that a *prima facie* case of obvious over the combination of Wold and Walczak has not been set forth because a person of ordinary skill in the art would not be provided any motivation to combine these references to practice the claimed invention.

Wold is said to disclose a replication competent adenoviral vector encoding the adenovirus death protein (ADP). Additionally, the Examiner states that "Wold does not specifically teach using expressing TRAIL from the adenovirus vector." Action, page 5, 3rd paragraph. However, in addition to not disclosing the use of TRAIL, Wold does not disclose the use of ***any transgene***. Furthermore, U.S. Serial No. 09/351,778, to which Wold claims priority and incorporates by referenece, clearly indicates that ***transgenes are***

to be expressed from replication-defective vectors and not from replication competent adenoviral vectors, particularly those that express ADP. "It is also contemplated that ADP-expressing viral vectors can be administered to neoplastic cells ***along with*** a replication defective virus that expresses an anti-cancer gene product." U.S. Serial No. 09/351,778, page 17, lines 22-24 (emphasis added). Thus, through its parent application, Wold actually teaches ***away*** from the incorporation of ***any*** transgene into a replication-competent adenoviral vector, and particularly an ADP-expressing virus.

Walczak fails to cure the deficiency of Wold with respect to motivation to practice the claimed invention. Simply put, Walczak does not even pertain to adenoviral vectors, instead simply disclosing that purified TRAIL ***protein*** can kill cancer cells (page 162, right column, 1st and 3rd paragraphs). As to the administration of gene encoding TRAIL to hyperproliferative cells, Walczak is silent, and thus is cannot begin to counter the teachings of Wold, set forth above.

In conclusion, the person of ordinary skill would not be motivated to combine Wold with Walczak, and if one were so motivated, the most it would produce would be the use of ***two vectors***, a replication-competent one coding for TRAIL, and a replication-defective one over-expressing ADP. Neither reference contemplates or suggests the use of transgenes such as TRAIL in replication-competent adenoviral vectors. Accordingly, it is submitted that claims 23-39, 41, 43-47 and 49 are not obvious over Wold taken with Walczak. Therefore, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103 be withdrawn.

2. The Rejection of Claims Over Henderson Taken with Griffith

Claims 23-38, 41, 43-47 and 49 have been rejected under 35 U.S.C. §103 over Henderson *et al.* (U.S. Patent 6,197,293) ("Henderson") taken with Griffith *et al.* (U.S. Patent 6,900,185) ("Griffith").

Henderson is said to disclose an E3-deleted adenovirus vector that expresses adenovirus genes in various configurations, under the control of prostate specific control sequences. Specifically, Henderson is directed to adenoviral vectors that contain a probasin transcriptional regulatory element to regulate gene expression or replication, and are therefore limited to the dorsolateral prostate and other androgen responsive tissues (see Henderson, column 5, lines 12-37). The vectors disclosed in Henderson are ***replication-competent***. Henderson discloses the presence of E1A and E1B coding sequences, which are required for replication competence, in a variety of embodiments. For example, Henderson discloses E1A and E1B under the control of the probasin transcriptional regulatory element (see Henderson, column 22, lines 32-61). Henderson also discloses vectors such as CN702 which contain the E1A and E1B region under the control of their native promoters (see Henderson, column 46, lines 15-16). Henderson does not disclose an adenoviral vector comprising a TRAIL coding region in combination with an ADP coding region.

Griffith, either alone or in combination with Henderson, does not provide the necessary motivation to one of skill in the art to practice the claimed invention. Griffith appears to provide a general teaching that administration of TRAIL via ***replication-defective*** viral vectors leads to tumor cell death. There is no suggestion or motivation found within Griffith for a skilled artisan to incorporate TRAIL into a ***replication-***

competent adenoviral vector. Unlike the functional E1 regions disclosed in Henderson, the Action states that "Griffith teaches deleting the E1 region of the adenovirus." Action, page 8, first paragraph. A deletion of the entire E1 region as taught by Griffith, renders the resultant adenoviral vector replication-defective. Such vectors must be propagated in trans-complementary cell lines such as 293 cells (see column 11, lines 20-35). Moreover, Griffith clearly indicates that replication-defective vectors are contemplated, stating "[i]n particular, the expression vector is a non-replicative adenovirus vector." Griffith, column 9, lines 47-48. Additionally, Griffith, in generating such vectors actively screened against replication competent adenovirus (column 11, lines 38-40). By stating a preference for only replication defective adenoviral vectors and actively screening against replication competent adenovirus, Griffith not only provides no motivation to combine the teachings of these references, but also ***teaches away*** from such a combination.

As each rejected dependent claim ultimately depends from claim 23, the combination of Henderson taken with Griffith cannot render these claims obvious. Accordingly, it is submitted that claims 23-38, 43-47 and 49 are not obvious over Henderson taken with Griffith. Therefore, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103 be withdrawn.

3. The Rejection of Claims Over Henderson Taken with Griffith and Further In View of Bruder

Claims 23 and 41 have been rejected under 35 U.S.C. §103 over Henderson taken with Griffith and further in view of Bruder *et al.*, *J. Virol.*, 71:7623-7628, 1997 ("Bruder"). As discussed above, the section, the combination of Henderson and Griffith

does not render obvious the presently claimed invention. Bruder fails to cure the deficiency of Henderson taken with Griffith. Bruder, like Griffith, also discloses ***replication-defective*** adenoviral vectors in which the entire E1 region is deleted and which are trans-complemented with 293 cells (see Bruder, page 7624, left column, "cells and viruses"). Accordingly, the combination of Henderson taken with Griffith in view of Bruder cannot render obvious claims 23 and 41. Therefore, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103 over Henderson taken with Griffith in view of Bruder be withdrawn.

D. Double Patenting Rejections

1. Provisional Rejections for Non-Statutory Obviousness-Type Double Patenting

a. Claims 1-75 of Copending Application 11/057,710

Claims 23-26, 32-38, 41, 43-47 and 49 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting. Because this rejection is provisional, Applicants will submit a terminal disclaimer, if necessary, once either application is otherwise allowable.

b. Claims 11-15, 20-22, 24, 32-44, 60-75 and 97-108 of Copending Application 09/351,778 In View of Walczak

Claims 23-26, 32-38, 41, 43-47 and 49 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting. Because this rejection is provisional, Applicants will submit a terminal disclaimer, if necessary, once either application is otherwise allowable.

c. Claims 28-72 of Copending Application 11/249,873 In View of Walczak

Claims 23-26, 32-38, 41, 43-47 and 49 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting. Because this rejection is provisional, Applicants will submit a terminal disclaimer, if necessary, once either application is otherwise allowable.

d. Over Claims 1-75 of Copending Application 11/057,710 In View of Walczak

Claims 23-26, 32-38, 41 and 43-47 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting. Because this rejection is provisional, Applicants will submit a terminal disclaimer, if necessary, once either application is otherwise allowable.

2. The Non-Provisional Rejections for Non-Statutory Obviousness-Type Double Patenting

The Action rejects claims 23-26, 32-34, 36-38, 41, 43-47 and 49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-11 of Wold, in view of Walczak. The Examiner contends that the claims in Wold differ form the instant claims by not specifically teaching the expression of Trail from an adenovirus vector. The Action further argues that Walczak teaches the tumoricidal activity of TRAIL. From this, the Action concludes that the combination is obvious.

Applicants point out that with a double-patenting rejection, only the claims of Wold are used for the rejection. MPEP §804. III ("One significant difference is that a double patenting rejection must rely on a comparison with the claims in an issued patent

or to be issued patent, whereas an obvious rejection based on the same patent under 35 U.S.C.§ 102(e)/103(a) relies on a comparison with what is disclosed (whether or not claimed) in the issued or to be issued patent"). Thus, the available content from Wold is even less than in the §103 rejection discussed above. So, just as with that rejection, the combination of Wold and Walczak would not lead one to created a single replication-competent adenoviral vector expressing ADP and TRAIL, but instead, would at most suggest the use of two vectors, one for each gene, with the latter being replication-defective. Thus, for the reasons given above, the present claims are not obvious in view of the claims in Wold combined with Walczak. Applicants respectfully request that this rejection be withdrawn.

E. Conclusion

Applicants believe that the present document is a full and complete response to the Office Action dated June 12, 2006. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. The Examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

III. PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. §1.136(a), Applicants petition for an extension of time of one month to and including October 12, 2006, in which to respond to the Office Action dated June 12, 2006. Pursuant to 37 C.F.R. § 1.17, a check in the amount of 60.00 is

enclosed, which is the process fee for a one-month extension of time. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/INRP:106US.

Respectfully submitted,

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Date: October 12, 2006